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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,593	BOWDISH ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,17-23,36,44,85-87,89 and 96-112* is/are pending in the application.

4a) Of the above claim(s) *17,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/11/06; 7/19/02; 8/18/03,
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 07/31/2006, and a response to the arguments is set forth.

2. Claims 4, 12-16, 24-35, 37-43, 45-84, 88 and 90-95 have been cancelled.

3. Claims 100-112 have been newly added.

4. Claims 1, 44, 85, 86, 96 and 99 have been amended.

5. Claims 17, 20 and 21 have been withdrawn.

6. Thus, claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 are under examination.

7. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

8. This office action consists of new grounds of rejections.

Rejections withdrawn

9. The rejection of claims 44, 85, 86, 87 and 89 under 35 U.S.C. 103(a) as obvious in light of Barbas et al (a) (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al (b) (PNAS 92:2529-2533, 1995) and in view of Kini et al (FEBS Letters, 1995. 375: 15-17) is withdrawn for the reasons below.

Kini et al teaches adding prolines to the ends of the short peptides but does not teach adding prolines to a peptide that is inserted into the middle of a large protein such

that the inserted proline has very long flanking sequences (as claimed in claims 44, 85, 86, 87 and 89); and thus does not suffice as appropriate prior art.

Futher, Barbas et al. (a) fails to teach or suggest that a dipeptide amino acid sequence should be introduced flanking the peptide.

In addition, the data presented by the applicant in the specification has been carefully considered upon which the examiner agrees with the applicant that it would not have been obvious to one of ordinary skill in the art to have produced the immunoglobulin molecule as claimed in claims 44, 85, 86, 87 and 89 in view of the above-cited references.

10. The rejection of claims 44, 85, 86, 87 and 89 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants arguments on page 13 of the response filed on 07/31/2006.

The applicants argue that the specification clearly describes and defines what is meant by a biological activity (page 13, lines 1-17 of the specification), in addition to providing numerous examples of biologically active peptides and thus one of ordinary skill in the art would clearly understand what is meant by the term "biologically active peptide".

Thus, the applicant's arguments are found persuasive and hence the 112/second rejection of claims 44, 85, 86, 87 and 89 is withdrawn.

11. The rejection of claims 44, 85, 86, 87 and 89 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94; cited in the previous office action mailed 10/18/2005) and further in view of Dower et al (WO 96/40750, published 12/96; cited in the previous office action mailed 10/18/2005) and Barbas et al (b) (PNAS 92:2529-2533, 1995; cited in the previous office action mailed 10/18/2005) and in view of Kini et al (FEBS Letters. 1995, 375:15-17; cited in the previous office action mailed 10/18/2005) and in view of Cwirla et al (Science, Vol, 276 13 June 1997; IDS 8.15.2005) and further in view of Wrighton et al. (Science. 1996. 273, 458-463) as evidenced by Helms (Protein Science. 1995, 4:2073-2081; cited in the previous office action mailed 08/20/2003) is withdrawn for the reasons below.

Kini et al teaches adding prolines to the ends of the short peptides but does not teach adding prolines to a peptide that is inserted into the middle of a large protein such that the inserted proline has very long flanking sequences (as claimed in claims 44, 85, 86, 87 and 89); and thus does not suffice as appropriate prior art.

Futher, Barbas et al. (a) fails to teach or suggest that a dipeptide amino acid sequence should be introduced flanking the peptide.

In addition, the data presented by the applicant in the specification has been carefully considered upon which the examiner agrees with the applicant that it would not have been obvious to one of ordinary skill in the art to have produced the immunoglobulin molecule as claimed in claims 44, 85, 86, 87 and 89 in view of the above-cited references.

Rejections Maintained

12. The rejection of claims 1-3, 5-11, 18, 19, 22, 23, 36, 96, 99, 100, 101 and 104-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94; cited in the previous office action mailed 10/18/2005) and further in view of Dower et al (WO 96/40750, published 12/96; cited in the previous office action mailed 10/18/2005) and Barbas et al (b) (PNAS 92:2529-2533, 1995; cited in the previous office action mailed 10/18/2005) and in view of Cwirla et al (Science, Vol, 276 13 June 1997; IDS 8.15.2005) and further in view of Wrighton et al. (Science. 1996. 273, 458-463) as evidenced by Helms (Protein Science. 1995, 4:2073-2081; cited in the previous office action mailed 08/20/2003) is maintained and made here within. Please note that this rejection has been modified to remove the Kini et al reference and therefore claims 44, 85, 86, 87 and 89 are no longer part of this rejection.

The applicant argues that the examiner merely added two additional references to the rejection but it appears to be the same rejection. The new references, Cwirla et al and Wrighton et al, merely disclose TPO and EPO peptide mimetics, and it has not been explained how these references change or advance the argument in comparison to the previous rejection which was withdrawn (please see page 14 3rd paragraph of the response filed on 07/31/2006).

In response to the above argument, the applicant is reminded that the previous rejection was withdrawn because the applicant amended the claims (in particular, claim 1) such that the claim reads "An immunoglobulin molecule or fragment

thereof.....wherein the immunoglobulin molecule or fragment thereof binds to and agonizes an EPO or TPO receptor". Thus, to cover the agonistic properties of the EPO and TPO peptide mimetics, Cwirla et al and Wrighton et al were included in the rejection because Cwirla teaches that the 14 amino acid TPO peptide that is 100 % identical to the TPO peptide as claimed can act as a potent agonist of the TPO and Wrighton et al teach small peptides as potent mimetics of the protein hormone EPO and show that the peptides act as agonists and stimulate erythropeoiesis in mice. Thus, the addition of these two references to the already cited art covers all the limitations as introduced in the claims in the previous amendments.

The applicants argue that Barbas et al (a) only discusses antagonists in contrast to the pending claims which are directed to agonists and further provide a reference to point out the differences between agonist and antagonistic properties.

Thus, once again, the examiner would like to remind the applicant the reason for which the references Cwirla et al and Wrighton et al were added to the previous rejection (please see above). Further, in view of the above argument, the applicant is directed to Example 1 in Barbas et al (a) wherein RGD-dependent human monoclonal antibodies a) anti-GPIIIb/IIIIA human monoclonal antibodies, b) anti-victronectin receptor antibodies and c) anti-HIV GP120 human monoclonal antibody; and in example 2 wherein non-RGD-dependent human monoclonal antibodies a) anti-GPIIIb/IIIIA human monoclonal antibodies and b) anti-victronectin receptor antibodies; and pages 75-79 clearly recite the antibodies wherein the antibodies can be used to *stimulate* or

agonize the receptor function and/or receptor mediated events. Thus, Barbas already suggest the replacement of CDRs that have agonistic properties.

Hence, in view of the above arguments and the clarification of the cited art, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the above teachings of Barbas et al (a) and Barbas et al (b) with Dower et al because Dower et al specifically teach peptides that are fusion proteins and that the peptides need to be constrained to be active.

Moreover, one of ordinary skill in the art would have known to use an antibody as a scaffold to present the TPO peptide because in solution peptides can be a random configuration and the scaffold constrains the peptide and presents it in a conformation that is better for binding and it would have been obvious to have residues flanking the sequence for presentation and it would have been obvious to use a proline at the C-terminus because of the teachings by Barbas et al (a) wherein Barbas et al (a) teach replacing CDRS in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for example (see page 5, 8, 17, lines 5-33, page 19-20, page 26-27, 28-29, 53, 144, 149) and as evidenced by Helms et al it is known in the art that proline residues decrease the conformational flexibility of a peptide (see page 2078) and thus would constrain the peptide.

Furthermore, it would have been obvious to place the peptide in a CDR because Barbas et al (a) teach human antibodies have benefits of therapy in vivo in humans for blocking or inhibiting the target and in view of Dower et al who teach that the TPO peptides can be used for therapy, one would have motivation to add the peptide to the antibody CDR and use as agonists as taught by Cwirla et al and Wrighton et al., because Cwirla teaches that the 14 amino acid TPO peptide that is 100 % identical to the TPO peptide as claimed can act as a potent agonist of the TPO and as a potent natural cytokine, and Wrighton et al, through random phage display isolate small peptides that bind to and activate the receptor for the cytokine EPO, and show that the peptides act as agonists and stimulate erythropeoiesis in mice.

Thus it would have been obvious to one skilled in the art to have produced the an immunoglobulin or fragment thereof comprising a region where amino acid residues corresponding to at least a proline of a CDR replaces with a peptide mimetic selected from the group of EPO and TPO, wherein the immunoglobulin molecule fragment thereof binds to and agonizes an EPO or TPO receptor, wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody.

In addition, the limitations as proposed in the newly added claims 100, 101, 104-112, the above cited references teach and further explain the significance of each and every limitation; wherein Barbas(a) et al teach replacing CDRs in a heavy or light chain of an antibody and suggest the replacement of one or more CDRs with biologically active peptides. Furthermore, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have generated an antibody or an

antigen binding fragment thereof wherein the one or two CDRs can be replaced in any of the six positions within the light or heavy chain variable regions, et al because Barbas et al (a) teach antibodies with several peptide sequences replacing the CDRs in an antibody and the molecules bind the target receptor and suggest that other sequences for other receptors would also work in replacing the CDRs (see pages 24-27, in particular) and the need to constraint the peptides (see pages 28-29, in particular).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

New Grounds of Rejections

13. Claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 86, 96 and 99 are not clear for reciting "....wherein one or more amino acid residues of each of a CDR are replaced with a peptide mimetic....". It is not clear if the applicant means that one CDR is replaced with one or two peptide mimetic(s) OR if one peptide mimetic is replaced for one and/or two CDRs; OR Does the applicant mean that the amino acid(s) with the CDR is/are substituted for a peptide mimetic? Appropriate correction is required.

14. Claim 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The amendments filed on 07.31.2006 introduced NEW MATTER in claims 1, 86, 96 and 99. Claims 1, 86, 96 and 99 recite "..... wherein one or more amino acid residues of a CDR are replaced with a peptide mimetic .....". Thus, the claims read on an immunoglobulin molecule or fragment thereof comprising a region wherein one or more amino acids within the CDR portion can be replaced one or more EPO mimetics OR one or more TPO mimetics OR a combination of one or more EPO and TPO receptors. However, the specification does not provide any support for such immunoglobulin as interpreted by the amendments. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should specifically point out the support for any amendments made to the disclosure.") The specification as originally filed discloses an immunoglobulin molecule or fragment thereof wherein one or more CDRs are replaced with: one EPO mimetic that binds to the erythropoietin receptor, one TPO mimetic that binds to the thrombopoietin receptor, both EPO mimetic or both TPO mimetics wherein the immunoglobulin molecule or fragment binds erythropoietin or thrombopoietin receptor respectively. However, neither the

specification nor the applicants arguments provide any support for the immunoglobulin molecule as claimed. Applicants are required to specifically point our where the support for the newly added claim limitations can be found in the originally filed specification or claims or remove the limitation from the claim.

15. Claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoglobulin molecule or fragment thereof wherein one or more CDRs are replaced with: one EPO mimetic that binds to the erythropoietin receptor, one TPO mimetic that binds to the thrombopoietin receptor, both EPO mimetic or both TPO mimetics wherein the immunoglobulin molecule or fragment binds erythropoietin or thrombopoietin receptor respectively, does not reasonably provide enablement for an immunoglobulin molecule or fragment that comprises the number of replacement of a CDR with an EPO or a TPO or both EPO or both TPO peptide mimetics that do not bind either of the receptors OR an immunoglobulin wherein one or more amino acid residues of each of a CDR are replaced with one of the peptide mimetics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an immunoglobulin or fragment comprising a region wherein amino acid residues corresponding to atleast a portion of a two complementarity determining regions (CDRs) are replaced with a peptide mimetic selected from the group consisting of an EPO mimetic and a TPO mimetic. Thus, the claims as written comprise an immunoglobulin wherein the CDRs are replaced with an EPO or a TPO mimetic or both that may or may not bind to the antigen. The specification teaches replacement of CDRs with the EPO and TPO sequences wherein the sequences are the same in the CDRs and the molecule binds the receptor (see Examples 3 and 5). The specification does not enable molecules that do not bind the receptor.

As evidenced from Dower et al (US Patent 5,869,451, issued 2/99) peptides for the EPO and TPO receptors are screened by using a screening method (see column 17-18 and Figures 3A-G, in particular) and these compounds can be used to treat patients. As such one skilled in the art would not know how to use an immunoglobulin or fragment thereof that do not bind to the receptor.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results.

Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979) teach that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function. Rudikoff et al. also teach that the alteration phosphocholine-binding function of a single amino acid in the CDR of a myeloma protein resulted in the loss of antigen-binding (please see the entire document, in particular)

Further, Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward

(page 2191, first column, lines 12-17 and second column, lines 3-8).

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-3, 5, 6, 7, 8, 18, 22, 23, 36, 44, 85, 97, 98, 99 and 100-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 5, 6, 8, 10, 11, 16, 26-35, 38-56 of copending Application No. 10/307,724. Although the conflicting claims are not identical, they are not patentably distinct from each other because Please see below.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 5, 6, 8, 18, 22, 23, 36, 44, 85, 97, 98, 99 and 100-112 of the instant application are drawn to an immunoglobulin molecule or fragment thereof comprising a regions wherein one or more amino acid residues of a complementarity determining region (CDR) are replaced with a peptide mimetic selected from the group consisting of erythropoietin (EPO) mimetics and thrombopoietin (TPO) mimetics, wherein the immunoglobulin molecule or fragment thereof binds to and agonizes an EPO or TPO receptor, further comprising at least one flanking sequence including at least one amino acid covalently linked to at least one end of the peptide mimetic wherein the at least one flanking sequence includes a flanking sequence having a proline that is covalently linked to the peptide mimetic, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment, wherein the immunoglobulin molecule is a full IgG molecule, wherein the CDR is located on a light chain, wherein the CDR is located on a heavy chain, wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain and a CDR2 of a light chain, wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and CDR2 of a heavy chain, wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and CDR1 of a light chain, wherein the TPO mimetic comprises the amino acid sequence set forth in SEQ. ID. NO. 1, wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid; in addition to a

composition comprising an immunoglobulin or fragment thereof according to claim 1 and a pharmaceutically acceptable carrier. The claims are further drawn to an immunoglobulin molecule or fragment thereof comprising a region wherein one or more amino acid residues of a CDR are replaced with a biologically active peptide flanked with a proline at the carboxy terminus of the biologically active peptide to create a resulting immunoglobulin molecule or fragment thereof, wherein said biologically active peptide has a biological activity and wherein the resulting immunoglobulin molecule or fragment thereof exhibits the biological activity of the biologically active peptide, wherein the biologically active peptide is flanked with a proline at its carboxy terminus and flanked with an amino acid sequence at its amino terminus. The claims are further drawn to an immunoglobulin molecule or fragment thereof according to claim 2 wherein the flanking sequence consists of two amino acids and an immunoglobulin molecule or fragment thereof according to claim 3 wherein the flanking sequence consists of two amino acids; further, an immunoglobulin molecule or fragment thereof comprising a region wherein one or more amino acid residues of a CDR are replaced with an agonist peptide mimetic, and wherein the resulting immunoglobulin molecule or fragment thereof binds to and agonizes a receptor. The claims are further drawn to an immunoglobulin molecule or fragment thereof according to claim 99 further comprising at least one flanking sequence including at least one amino acid covalently linked to at least one end of the peptide mimetic, wherein the at least one flanking sequence includes a flanking sequence having a proline that is covalently linked to the peptide mimetic, wherein the flanking sequence consists of two amino

acids, wherein the flanking sequence consists of two amino acids, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment.

Claims 1, 2, 3, 4, 5, 6, 8, 11, 16, 26-35, 38-56 of copending Application No. 10/307,724 (US '724) are drawn to an immunoglobulin molecule or fragment thereof comprising a region wherein amino acid residues corresponding to two complementarity determining regions (CDRs) are replaced with either two EPO mimetics or TPO mimetics, further comprising at least one flanking sequence including at least one amino acid covalently linked to atleast one end of atleast one peptide mimetic, wherein the flanking region includes a flanking sequence having a proline that is covalently linked to the peptide mimetic, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment, or a full IgG molecule, wherein the two CDRs are both located on a heavy chain, wherein the CDRs are a CDR3 of a heavy chain and a CDR2 or a heavy chain, wherein the immunoglobulin molecule or fragment thereof is human, anti-tetanus toxoid, and a composition comprising an immunoglobulin or fragment thereof according to claim 1 and a pharmaceutically acceptable carrier. The claims are further limited to an immunoglobulin wherein the TPO mimetic comprises SEQ ID NO:1. The claims are further drawn to an Immunoglobulin molecule or fragment thereof according to claim 1 wherein the CDRs are both located on a light chain, wherein one CDR is located on a heavy chain and one CDR is located on a light chain, wherein the CDRs are selected

from the group consisting of CDR2 and CDR3, wherein at least one of the CDRs is located in a heavy chain, wherein at least one of the CDRs is located in a light chain, wherein one CDR is a CDR2 and one CDR is a CDR3, wherein the CDRs are selected from the group consisting of heavy chain CDR3-1ight chain CDR3, heavy chain CDR3-heavy chain CDR2, light chain CDR3-1ight chain CDR2, heavy chain CDR3-1ight chain CDR2, heavy chain CDR3-heavy chain CDR2-1ight chain CDR2, and heavy chain CDR2-1ight chain CDR2, wherein the CDRs are heavy chain CDR3 and light chain CDR1, wherein both CDRs are replaced with EPO mimetics, wherein both CDRs are replaced with TPO mimetics, wherein at least one peptide mimetic is flanked with a proline at the carboxy terminus, wherein the flanking sequence consists of two amino acids, wherein the flanking sequence consists of two amino acids, wherein the two peptide mimetics are identical, wherein one or more amino acid residues of each of two complementarity determining regions (CDRs) are replaced with an agonist peptide mimetic and wherein the immunoglobulin molecule or a fragment thereof binds to and agonizes a receptor, further comprising at least one flanking sequence comprising at least one amino acid covalently linked to at least one end of at least one agonist peptide mimetic, wherein the at least one flanking sequence comprises a proline that is covalently linked to at least one peptide mimetic, wherein the flanking sequence consists of two amino acids, wherein the flanking sequence consists of two amino acids, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment, wherein the immunoglobulin molecule is a full IgG molecule, wherein both CDRs are located on a heavy chain,

wherein both CDRs are located on a light chain, wherein one CDR is located on a heavy chain and one CDR is located on a light chain, wherein the CDRs are a CDR2 and a CDR3, wherein the two peptide mimetics are identical, wherein the immunoglobulin molecule or fragment thereof is human, wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid and a composition comprising an immunoglobulin or fragment thereof.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the immunoglobulin as claimed, please see below.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced immunoglobulin molecule or fragment as claimed in claims 1-3, 44 and 85 of the instant application, because claims 1-3 of the co-pending application US '724 are drawn to an immunoglobulin molecule or fragment thereof comprising a region wherein amino acid residues corresponding to two complementarity determining regions (CDRs) are replaced with either two EPO mimetics or TPO mimetics, further comprising at least one flanking sequence including at least one amino acid covalently linked to atleast one end of atleast one peptide mimetic, wherein the flanking region includes a flanking sequence having a proline that is covalently linked to the peptide mimetic.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced an immunoglobulin molecule as claimed in claims 5, 6 and 8 of the instant application, because claims 4-6 of the co-pending application US '724 are drawn to an immunoglobulin molecule wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment, or a full IgG molecule, wherein the two CDRs are both located on a heavy chain.

Moreover, one of ordinary skill in the art would have known to produce an immunoglobulin molecule as claimed in claims 18, 22, 23 and 36 of the instant application because claims 8, 10, 11 and 16 of the co-pending application US '724 are drawn to an immunoglobulin or fragment thereof according to claim 1 wherein the TPO mimetic comprises SEQ ID NO:1, wherein the immunoglobulin or fragment thereof is human, wherein the immunoglobulin or fragment thereof is anti-tetanus toxoid and further a composition comprising an immunoglobulin or fragment thereof according to claim 1 and a pharmaceutically acceptable carrier.

Furthermore, one of ordinary skill in the art would have known to produce an immunoglobulin molecule as claimed in claims 97-112 of the instant application, because claims 26-35, 38-56 of the co-pending application US '724 are drawn to an immunoglobulin or fragment thereof according to claim 1 wherein the CDRs are both located on a light chain, wherein one CDR is located on a heavy chain and one CDR is located on a light chain, wherein the CDRs are selected from the group consisting of CDR2 and CDR3, wherein at least one of the CDRs is located in a heavy chain, wherein

at least one of the CDRs is located in a light chain, wherein one CDR is a CDR2 and one CDR is a CDR3, wherein the CDRs are selected from the group consisting of heavy chain CDR3-light chain CDR3, heavy chain CDR3-heavy chain CDR2, light chain CDR3-light chain CDR2, heavy chain CDR3-light chain CDR2, heavy chain CDR3-heavy chain CDR2-light chain CDR2, and heavy chain CDR2-light chain CDR2, wherein the CDRs are heavy chain CDR3 and light chain CDR1, wherein both CDRs are replaced with EPO mimetics, wherein both CDRs are replaced with TPO mimetics wherein at least one peptide mimetic is flanked with a proline at the carboxy terminus, wherein the flanking sequence consists of two amino acids, wherein the flanking sequence consists of two amino acids, wherein the two peptide mimetics are identical, wherein one or more amino acid residues of each of two complementarity determining regions (CDRs) are replaced with an agonist peptide mimetic and wherein the immunoglobulin molecule or a fragment thereof binds to and agonizes a receptor, further comprising at least one flanking sequence comprising at least one amino acid covalently linked to at least one end of at least one agonist peptide mimetic, wherein the at least one flanking sequence comprises a proline that is covalently linked to at least one peptide mimetic, wherein the flanking sequence consists of two amino acids, wherein the flanking sequence consists of two amino acids, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and scFv fragment, wherein the immunoglobulin molecule is a full IgG molecule, wherein both CDRs are located on a heavy chain, wherein both CDRs are located on a light chain, wherein one CDR is located on a heavy chain and one CDR is

located on a light chain, wherein the CDRs are a CDR2 and a CDR3, wherein the two peptide mimetics are identical, wherein the immunoglobulin molecule or fragment thereof is human, wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid and a composition comprising an immunoglobulin or fragment thereof.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Thus, claims 1-3, 5, 6, 7, 8, 18, 22, 23, 36, 44, 85 and 97-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 5, 6, 8, 10, 11, 16, 26-35 and 38-56 of copending Application No. 10/307,724.

Conclusion

17. No claims are allowed

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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Sheela G. Huff
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PRIMARY EXAMINER